Age and sex and glucose-lowering drug efficacy

Analysis of the impact of age on treatment interactions suggests that SGLT2 inhibitors are more cardioprotective, despite producing smaller reductions in HbA_{1c}, in older versus younger people, according to this network meta-analysis published in *JAMA*. Conversely, GLP-1 receptor agonists were shown to be more cardioprotective in younger rather than older people, despite being associated with greater HbA_{1c} reductions with increasing age, when used as monotherapy or dual therapy. SGLT2 inhibitor and GLP-1 RAs were both associated with a lower risk of major adverse cardiovascular events but there was no such association with DPP-4 inhibitor use. There was no evidence of a sex × treatment interaction for SGLT2 inhibitors or GLP-1 RAs, and no age or sex interaction with any of the three treatment classes in relation to adverse events or hypoglycaemia.

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It is now well established that newer drugs for type 2 diabetes, such as DPP-4 inhibitors, SGLT2 inhibitors and GLP-1 receptor agonists, are effective at lowering glucose, and that the SGLT2 inhibitors and some GLP-1 RAs reduce the risk of major adverse cardiovascular events (MACE). Although subgroup analyses of the cardiovascular outcome trials have explored the potential impacts of age, sex, ethnicity and many other characteristics of the trial participants, it remains unclear whether the glucose-lowering and cardiovascular benefits of these drug classes vary by age and sex, and this is important in guiding us when supporting people to make decisions regarding treatment choices.

Network meta-analysis

This network meta-analysis by UK and global diabetes experts used individual and aggregate data from identified randomised controlled trials of DPP-4 inhibitors, SGLT2 inhibitors and GLP-1 RAs, compared with placebo or active comparators, in people with type 2 diabetes (Hanlon et al, 2025). The study was part of a larger project and the current paper presents the results of age and treatment interactions and age and sex interactions only. Nearly 600 trials looking at glucose-lowering efficacy (309 503 participants) and 23 trials exploring MACE (168 489 participants) were included, with 14 trials looking at both HbA_{1c} and MACE. The drug interactions with age and sex were explored when the drug classes were used as monotherapy, dual therapy or triple therapy.

Results

Overall treatment effects on HbA_{1c} varied between 0.5% to 1.5% (5–16 mmol/mol) reductions across the three drug classes, and reductions in MACE were observed with SGLT2 inhibitors and GLP-1 RAs but not with DPP-4 inhibitors.

DPP-4 inhibitors were associated with slightly better reductions in HbA_{1c} in older people when used as dual therapy, but not when used as monotherapy or triple therapy. As MACE benefits were not demonstrated with DPP-4 inhibitors, associations between this class and age and sex presented in the paper should be viewed with caution.

GLP-1 RAs were associated with greater reductions in HbA_{1c} as age increased, both for monotherapy and for dual therapy, but not when used as triple therapy.

SGLT2 inhibitors were associated with modest reductions in glucose-lowering efficacy with increasing age, with comparative effects versus placebo reduced by a quarter at age 75 versus 45 years. The authors postulate that this was likely related to reduced renal function in the older population.

Despite lesser reductions in HbA_{1c} at older ages, SGLT2 inhibitors were associated with greater reductions in MACE in older age

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groups. Conversely, despite having greater glucose-lowering effects in older ages, GLP-1 RAs were associated with lesser reductions in MACE in older age groups, with the greatest impact on MACE demonstrated in younger and female participants.

There was a small difference in efficacy favouring males when SGLT2 inhibitors were used as triple therapy, but overall no sex × treatment interaction was seen with SGLT2 inhibitors or GLP-1 RAs.

Rates of gastrointestinal adverse events, hypoglycaemia and urinary tract infections did not vary according to age or sex for any of the three classes of drugs. There were no age × treatment or sex × treatment interactions with any of the three drug classes for all-cause mortality.

Discussion

The observation of a greater impact of SGLT2 inhibitors on MACE in older people despite a lesser impact on reducing HbA_{1c} is consistent with the MACE benefits seen in people with conditions such as heart failure and chronic kidney disease even in the absence of type 2 diabetes.

There were few people over 80 years of age included in the clinical trials identified in this meta-analysis and, furthermore, the analysis did not consider frailty of older participants; therefore, effects seen in this study should not be extrapolated to older, frailer groups, in whom the drugs may be used in routine practice.

The authors outline several limitations of this study. Individual participant data was not available for all the studies included, and aggregate data was used for all treatment comparisons. Despite a large number of studies being included in the analysis, only a small number of these (including the cardiovascular outcome trials for the individual drugs) assessed effects on MACE. Renal outcomes were not presented in this analysis, even though some studies explored them, and the authors chose to present MACE data as relative rather than absolute risks.

Implications for practice

We already individualise our advice on glucose-lowering medication to the people with type 2 diabetes we see. Increasingly, we are prioritising use of SGLT2 inhibitors and GLP-1 RAs for the additional benefits they provide over and above their glucose-lowering effects. Recently, a useful tool from the Mastermind Consortium has been published (Dennis et al, 2025), which can help us to choose the drug which is likely to be most effective at glucose lowering over the next 12 months. The findings from the current study can be used alongside that tool to help guide evidence-based discussions with people with type 2 diabetes.

This study reminds us that, although more relaxed HbA_{1c} targets are recommended for older people with type 2 diabetes, we should remain mindful of the significant cardioprotective benefits that SGLT2 inhibitors and GLP-1 RAs may provide even if these drugs are not required for glucose lowering in people already at their agreed HbA_{1c} target. Guidelines reinforce that we should consider initiating SGLT2 inhibitors or GLP-1 RAs for cardiorenal protection as soon as cardiovascular disease, heart failure or chronic kidney disease are diagnosed, without waiting for the next review.

This new information brings us another step closer to being able to deliver personalised medicine to the people with type 2 diabetes we support in our daily practice. ■

Dennis JM, Young KG, Cardoso P et al; MASTERMIND Consortium (2025) A five-drug class model using routinely available clinical features to optimise prescribing in type 2 diabetes: A prediction model development and validation study. *Lancet* **405**: 701–14

Hanlon P, Butterly E, Wei L et al (2025) Age and sex differences in efficacy of treatments for type 2 diabetes: A network meta-analysis. *JAMA* **333**: 1062–73

Practice points

1. SGLT2 inhibitors appear to have greater cardiovascular benefits despite having lesser glycaemic effects in older versus younger people, while GLP-1 RAs have greater cardioprotective effects but relatively lower glycaemic efficacy in younger people.
2. Consider initiating SGLT2 inhibitors or GLP-1 RAs for cardiorenal protection as soon as cardiovascular disease, heart failure or chronic kidney disease are diagnosed.
3. These findings can be used alongside the tool from the Mastermind Consortium to aid decisions on which glucose-lowering agents to prescribe.